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SYSTEMIC PHARMACOLOGY

Malaria sickens and kills people through several pathological mechanisms, understood to varying degrees. In addition to first- and second-line antimalarial drug treatments, adjunctive and supportive care measures (e.g., intravenous fluids, blood transfusions, supplemental oxygen, antiseizure medications) may be needed for severe manifestations. The aims of treatment are to prevent death or long-term deficits from malaria, to cut short the morbidity of an acute episode of illness, and to clear the infection entirely so that it does not recur.

Fever, sweating, and chills (or, in some cases, merely fever) triggered by the release of

plasmodia into the bloodstream from mature blood schizonts, are the most common symptoms heralding the onset of a clinical case of uncomplicated falciparum malaria. Without treatment—or an active immune response primed by repeated previous malaria infections—the number of parasites will increase with every 2-day cycle of reproduction. A mature infection may involve up to 1012 circulating plasmodia.
At any time after the infection is established, the vast majority of plasmodia will be in some stage of asexual maturation leading to another round of multiplication within the patient's bloodstream. However, a few parasites will have transformed into sexual stages (gametocytes) that, once ingested by mosquitoes, can perpetuate the transmission cycle. Because each stage of the malarial life cycle exhibits distinct biochemical and other

characteristics (i.e., it expresses different proteins or locates in different sites within the body), a drug may kill one stage but have little effect on another. In other words, in each life-cycle stage the parasite manifests unique biological properties that can offer a target for the action of one or more antimalarial drugs.

ANTIMALARIAL DRUG CLASSES

Anti malarial drugs can be classified according to anti malarial activity and according to structure.

1. According to anti malarial activity:

1. Tissue schizonticides for causal prophylaxis: These drugs act on the primary tissue forms of the plasmodia which after growth within the liver, initiate the erythrocytic stage. By blocking this stage, further development of the

infection can be theoretically prevented. Pyrimethamine and Primaquine have this activity. However since it is impossible to predict the infection before clinical symptoms begin, this mode of therapy is more theoretical than practical.

2. Tissue schizonticides for preventing relapse: These drugs act on the hypnozoites of P. vivax and P. ovale in the liver that cause relapse of symptoms on reactivation. Primaquine is the prototype drug; pyrimethamine also has such activity.
3. Blood schizonticides: These drugs act on the blood forms of the parasite and thereby terminate clinical attacks of malaria. These are the most important drugs in anti malarial chemotherapy. These include chloroquine, quinine, mefloquine,

halofantrine, pyrimethamine, sulfadoxine, sulfones, tetracyclines etc.

4. Gametocytocides: These drugs destroy the sexual forms of the parasite in the blood and thereby prevent transmission of the infection to the mosquito. Chloroquine and quinine have gametocytocidal activity against P. vivax and P. malariae, but not against P. falciparum. Primaquine has gametocytocidal activity against all plasmodia, including P. falciparum.
5. Sporontocides: These drugs prevent the development of oocysts in the mosquito and thus ablate the transmission. Primaquine and chloroguanide have this action.

Thus in effect, treatment of malaria would include a blood schizonticide, a gametocytocide

and a tissue schizonticide (in case of P. vivax and P. ovale). A combination of chloroquine and primaquine is thus needed in ALL cases of malaria.

2. According to the structure:
    1. Aryl amino alcohols: Quinine, quinidine (cinchona alkaloids), mefloquine, halofantrine.
    2. 4-aminoquinolines: Chloroquine, amodiaquine.
    3. Folate synthesis inhibitors: Type 1 – competitive inhibitors of dihydropteroate synthase – sulphones, sulphonamides; Type 2 – inhibit dihydrofolate reductase – biguanides like proguanil and chloroproguanil; diaminopyrimidine like pyrimethamine
    4. 8-aminoquinolines: Primaquine, WR238, 605
    5. Antimicrobials: Tetracycline, doxycycline, clindamycin,

azithromycin, fluoroquinolones

6. Peroxides: Artemisinin (Qinghaosu) derivatives and analogues – artemether, arteether, artesunate, artelinic acid
7. Naphthoquinones: Atovaquone
8. Iron chelating agents: Desferrioxamine

Basic Properties of Antimalarials: Pharmacokinetics and Pharmacodynamics

The interactions of drugs with people who take them—how the compounds are absorbed, metabolized, distributed, and excreted—is referred to as pharmacokinetics. Antimalarial drugs differ considerably in their pharmacokinetics, which affect how well they work, how they are

dosed, and how long they must be taken. People also vary in how they respond to drugs. Some of these responses are genetically determined, others by health status, others by dietary factors. In general, the pharmacokinetic properties of the antimalarials are similar in children and adults, although the metabolism of several drugs is altered in pregnancy (e.g., atovaquone, mefloquine, cycloguanil
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A key pharmacokinetic property of antimalarials is how long they remain in the body. Artemisinin and its derivatives are absorbed and eliminated the most rapidly (half-life = 1 hour or less). Quinine also is absorbed and eliminated within one parasite life cycle (11 hours in healthy subjects to 18 hours in those with severe malaria). Other antimalarials are eliminated very slowly, remaining in significant concentrations for several days (pyrimethamine, halofantrine, lumefantrine, atovaquone), or even weeks (mefloquine, chloroquine, and piperaquine). In general, rapidly

eliminated drugs (artemisinin, and quinine) must be taken over four asexual cycles (7 days) to ensure cure in nonimmune patients. In contrast, drugs that are eliminated slowly require fewer doses over shorter periods because they remain active in the body.

Halofantrine, lumefantrine, atovaquone and, to a much lesser extent, mefloquine, are hydrophobic and lipophilic (i.e., insoluble in water and capable of dissolving in fat); as a result, their absorption also varies according to the amount of dietary fat consumed. For this reason, blood concentrations of these drugs may vary considerably from one individual to another following the same dose.

Pharmacodynamics

The way drugs act on their target —in this case, plasmodia—is called pharmacodynamics. The principal effect of antimalarial

drugs in uncomplicated malaria is to inhibit parasite multiplication by killing parasites. If an untreated infection progressed at maximum efficiency, with each life cycle, the total body parasite load would increase by a multiplication factor approximating the average number of viable parasites in a mature schizont (18-36) (White, 1997). Proliferation of parasites in nonimmune individuals often proceeds at multiplication rates of 6 to 20 per 2-day cycle (30-80 percent efficiency). Antimalarial drugs exerting maximum effect (Emax), on the other hand, reduce total parasite numbers 10- to 10,000-fold per cycle. Individual antimalarial drugs differ in their Emax (i.e., the proportion of total plasmodia killed per treatment); for example, artemisinins often yield a 10,000-fold reduction per asexual cycle, whereas antimalarial antibiotics

such as tetracycline or clindamycin may only achieve a 10-fold parasite reduction per cycle. The lowest blood or plasma concentration of an antimalarial drug that results in Emax can be considered a “minimum parasiticidal concentration” (MPC). Parasite reduction appears to be a first-order process throughout (Day et al., 1996), which means that a fixed fraction of the infecting malaria parasite population is removed with each successive cycle as long as the MPC is exceed.

Chloroquine

Chloroquine is the prototype anti malarial drug, most widely used to treat all types of malarial infections. It is also the cheapest, time tested and safe anti malarial agent.

Mechanism of action: The mechanism of action of

chloroquine is unclear. Being alkaline, the drug reaches high concentration within the food vacuoles of the parasite and raises its pH. It is found to induce rapid clumping of the pigment. Chloroquine inhibits the parasitic enzyme heme polymerase that converts the toxic heme into non-toxic hemazoin, thereby resulting in the accumulation of toxic heme within the parasite. It may also interfere with the biosynthesis of nucleic acids. Other mechanisms suggested include formation of drug-heme complex, intercalation of the drug with the parasitic DNA etc.

Absorption, fate and excretion: 90% of the drug is absorbed from G.I.T and rapidly absorbed from intra muscular and subcutaneous sites. It has a large distribution volume due to extensive sequestration in tissues of liver, spleen, kidney, lung etc. Hence the need for a larger

loading dose. Therapeutic blood levels persist for 6-10 days and elimination half-life is 1-2 months. Half of the drug is excreted unchanged by the kidneys, remaining is converted to active metabolites in the liver.

Anti malarial activity: It is highly effective against erythrocytic forms of P. vivax, P. ovale and P. malariae, sensitive strains of P. falciparum and gametocytes of P. vivax. It rapidly controls acute attack of malaria with most patients becoming afebrile within 24-48 hours. It is more effective and safer than quinine for sensitive cases.

Adverse effects: Chloroquine is a relatively safer anti malarial. At therapeutic doses, it can cause dizziness, headache, diplopia, disturbed visual accomodation, dysphagia, nausea, malaise, and pruritus of palms, soles and scalp. It can also cause visual hallucinations, confusion, and

occasionally frank psychosis. These side effects do not warrant stoppage of treatment. It can exacerbate epilepsy. When used as prophylactic at 300 mg of the base/ week, it can cause retinal toxicity after 3-6 years (i.e. after 50-100 g of chloroquine). Intra muscular injections of chloroquine can cause hypotension and cardiac arrest, particularly in children.

Contra indications: Chloroquine should be used with caution in patients with hepatic disease, (even though it is not hepatotoxic per se, it is distributed widely in the liver and is converted to active metabolites there; hence the caution), severe gastro intestinal, neurological or blood disorders. The drug should be discontinued in the event of such problems during therapy.

It should not be co-administered with gold salts and phenyl butazone, because all the three

can cause dermatitis. Chloroquine may interfere with the antibody response to human diploid cell rabies vaccine.

Quinine

Quinine is the chief alkaloid of cinchona bark (known as 'Fever Bark'), a tree found in South America. It has a colourful history of more than 350 years. Calancha, an Augustinian monk of Lima, first wrote about the curative properties of cinchona powder in "fevers and tertians" as early as in 1633. By 1640, the bark had already found its way into Europe, thanks to the Jesuit fathers (hence the name 'Jesuit's bark'). Eminent philosopher Cardinal de Lugo popularised the bark in Rome (hence it is also called Cardinal's bark). In 1820, Pelletier and Caventou isolated quinine and cinchonine from cinchona. Even today, quinine is obtained entirely from the natural

sources due the difficulties in synthesising the complex molecule.

Mechanism of action: Quinine acts as a blood schizonticide although it also has gametocytocidal activity against P. vivax and P. malariae. Because it is a weak base, it is concentrated in the food vacuoles of P. falciparum. It is said to act by inhibiting heme polymerase, thereby allowing accumulation of its cytotoxic substrate, heme.

As a schizonticidal drug, it is less effective and more toxic than chloroquine. However, it has a special place in the management of severe falciparum malaria in areas with known resistance to chloroquine.

Absorption, fate and excretion: Quinine is readily absorbed when given orally or intramuscularly. Peak plasma concentrations are achieved

within 1 – 3 hours after oral dose and plasma half-life is about 11 hours. In acute malaria, the volume of distribution of quinine contracts and clearance is reduced, and the elimination half-life increases in proportion to the severity of the illness. Therefore, maintenance dose of the drug may have to be reduced if the treatment is continued for more than 48 hours. The drug is extensively metabolised in the liver and only 10% is excreted unchanged in the urine. There is no cumulative toxicity on continued administration.

Adverse effects: Quinine is a potentially toxic drug. The typical syndrome of quinine side effects is called as cinchonism and it can be mild in usual therapeutic dosage or could be severe in larger doses. Mild cinchonism consists of ringing in the ears, headache, nausea and disturbed vision. Functional impairment of

the eighth nerve results in tinnitus, decreased auditory acuity and vertigo. Visual symptoms consist of blurred vision, disturbed colour perception, photophobia, diplopia, night blindness, and rarely, even blindness. These changes are due to direct neurotoxicity, although vascular changes may contribute to the problem.

Gastrointestinal symptoms like nausea, vomiting, abdominal pain and diarrhoea may be seen. Rashes, sweating, angioedema can occur. Excitement, confusion, delirium are also seen in some patients. Coma, respiratory arrest, hypotension, and death can occur with over dosage. Quinine can also cause renal failure. Massive hemolysis and hemoglobinuria can occur, especially in pregnancy or on repeated use.

Hypoprothrombinemia,

agranulocytosis are also reported.

Quinine has little effect on the heart in therapeutic doses and hence regular cardiac monitoring is not needed. However it can cause hypotension in the event of overdose.

Quinine reduces the excitability of the motor end plate and thus antagonises the actions of physostigmine. It can cause respiratory distress and dysphagia in patients of myasthenia gravis.

Quinine stimulates insulin secretion and in therapeutic doses it can cause hypoglycemia. This can be more severe in patients with severe infection and in pregnancy. Hypoglycemia in malaria may go unnoticed and could even cause death. Therefore, it is advisable to monitor blood glucose levels at least once in 4-6 hours while quinine is administered,

especially in severe infection and in pregnancy. Quinine induced hypoglycemia can recur even after administration of 25% or 50% dextrose. In such situations, maintenance with a 10% dextrose infusion is advisable. Resistant hypoglycemia due to quinine can be managed with Injection Octreotide, 50 microgram subcutaneously, every 6 to 8 hours.

Contraindications:
Hypersensitivity in the form of rashes, angioedema, visual and auditory symptoms are indications for stopping the treatment. It is contraindicated in patients with tinnitus and optic neuritis. It should be used with caution in patients with atrial fibrillation. Hemolysis is indication for immediately stopping the drug. It is also contraindicated in patients suffering from myasthenia gravis.

Chloroguanide (Proguanil)

More popularly known as proguanil, this drug was developed by British antimalarial research in 1945. It is a biguanide derivative that is converted to an active metabolite called cycloguanil pamoate. It exerts its antimalarial action by inhibiting parasitic dihydrofolate reductase enzyme. It has causal prophylactic and suppressive activity against P. falciparum and cures the acute infection. It is also effective in suppressing the clinical attacks of vivax malaria. However it is slower compared to 4-aminoquinolines.

Chloroguanide is slowly but adequately absorbed from the gastrointestinal tract. Peak plasma levels are attained within 5 hours and elimination half-time is about 16-20 hours.

Chloroguanide is available as tablets, each containing 100 mg

of the drug. The dose for prophylaxis is 100-200 mg daily. Chloroguanide along with chloroquine is used as prophylaxis effective against P. falciparum malaria.

Sulfadoxine+Pyrimethamine

Pyrimethamine and sulphadoxine are very useful adjuncts in the treatment of uncomplicated, chloroquine resistant, P. falciparum malaria. It is now used in combination with artesunate for the treatment of P. falciparum malaria. It is also used in intermittent treatment in pregnancy (IPTp)
Anti malarial activity:
Pyrimethamine inhibits the dihydrofolate reductase of plasmodia and thereby blocks the biosynthesis of purines and pyrimidines, which are so essential for DNA synthesis and

cell multiplication. This leads to failure of nuclear division at the time of schizont formation in erythrocytes and liver.
Sulfadoxine inhibits the utilisation of para-aminobenzoic acid in the synthesis of dihydropteroic acid. The combination of pyrimethamine and sulfa thus offers two step synergistic blockade of plasmodial division.

Absorption, fate and excretion: Pyrimethamine is slowly but completely absorbed after oral administration and is eliminated slowly with a plasma half-life of about 80-95 hours. Suppressive drug levels may be found in the plasma for up to 2 weeks. The drug is excreted in breast milk.
Sulfonamides are rapidly absorbed from the gut and are bound to plasma proteins. They are metabolised in the liver and are excreted in the urine. They

pass through the placenta freely. Sulfadoxine is a long acting sulfonamide with a half-life of 7-9 days.

Toxicity and contraindications:
Pyrimethamine can cause occasional skin rashes and depression of hematopoiesis. Excessive doses can produce megaloblastic anemia. Sulfonamides can cause numerous adverse effects. Agranulocytosis; aplastic anemia; hypersensitivity reactions like rashes, fixed drug eruptions, erythema multiforme of the Steven Johnson type, exfoliative dermatitis, serum sickness; liver dysfunction; anorexia, vomiting and acute hemolytic anemia can also occur. The drug is contraindicated in patients with known hypersensitivity to sulfa, infants below 2 months of age, patients with advanced renal

disease and first and last trimesters of pregnancy.

Mefloquine

Mefloquine was born during the Vietnam war, as a result of research into newer anti malarials, to protect the American soldiers from the multi drug resistant falciparum malaria. Nothing much has happened after that and hence this 'new' drug should be restricted for use against multi drug resistant falciparum only.

Anti malarial activity:

Mefloquine has been found to produce swelling of the P. falciparum food vacuoles. It may act by forming toxic complexes with free heme that damage membranes and interact with other plasmodial components. It is effective against the blood forms of falciparum malaria, including the chloroquine resistant types.

Absorption, fate and

excretion: Mefloquine is available for oral administration only because parenteral preparations cause severe local reactions. It is absorbed rapidly and is extensively bound to plasma proteins. Elimination half-life is about 2-3 weeks. It is mainly excreted in the faeces. Toxicity: It is generally well tolerated in therapeutic doses up to 1500 mg. Nausea, vomiting, abdominal pain and dizziness can occur in doses exceeding 1 g. Less frequently it can cause nightmares, sleeping disturbances, dizziness, ataxia, sinus bradycardia, sinus arrhythmia, postural hypotension, and an 'acute brain syndrome' consisting of fatigue, asthenia, seizures and psychosis. Mefloquine should be used with caution in patients with heart block, patients taking beta blockers, patients with history of epilepsy and psychiatric disease.

It should be avoided in first trimester of pregnancy and pregnancy should be avoided within 3 months of taking the drug.

Contraindications: It should not be used for prophylaxis in pregnancy, particularly during the first trimester. It is contraindicated in patients with history of seizures, severe neuropsychiatric disturbances, or adverse reactions to quinoline antimalarials like chloroquine and quinine. It should not be used concomitantly with these drugs for increased risk of cardiotoxicity and risk of convulsions. Mefloquine is reported to increase the risk of seizures in patients taking valproate. It may compromise adequate immunisation by live typhoid vaccine. Patients taking mefloquine should refrain from driving or operating machinery.